are protected from the activity of dipetidyl peptidase IV (DPP IV) and are administered by pulmonary means. Support for these claims can be found throughout the specification and in particular from page 9, line 26 to page 10, line 2. Applicants also submit new dependent Claims 71, 72, 103, 104, 113 and 114 directed to specified GLP-1 molecules that are protected from the activity of DPP IV and are administered by pulmonary means. Support for these claims can be found throughout the specification and in particular from page 8, line 1 to line 17. Dependent Claims 73 through 101, 105 through 111, and 115 through 121 originally depended from the as filed genus claims, but now they depend from the genus of DPP IV protected GLP-1 molecules.

REJECTION UNDER 35 U.S.C. § 112 FIRST PARAGRAPH

The Examiner rejected Claims 23 and 33 under 35 U.S.C. §112 first paragraph as containing subject matter that was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. Although the Examiner stated that Applicants have shown Val^8-GLP-1 can be administered to the lungs, and that certain antigenic determinants of the peptide appear in the serum, the Examiner argues that Applicant's immunoassay does not establish that intact peptide appears in serum and that there is no evidence that the peptide is 'useful' when delivered by pulmonary means. Applicants respectfully submit that this rejection is inappropriate and request reconsideration and withdrawal of the rejection.

The burden is on the Examiner to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). See also MPEP § 2164.04. In examining a patent application, the PTO is required to assume that the

specification complies with the enablement provision of § 112 unless it has acceptable evidence or reasoning to suggest otherwise. *In re Marzocchi*, 439 F.2d 220, 223, 169 USPQ 367, 369-370 (C.C.P.A. 1971).

> [I]t is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement.

Id. at 224.

Additionally, the Examiner suggests that Applicants have failed to prove that the peptide is 'useful' when delivered by pulmonary means and thus, have failed to enable their invention. "[The Examiner] should not impose a 35 U.S.C. § 112, first paragraph, rejection grounded on a 'lack of utility' basis unless a 35 U.S.C. § 101 rejection is proper." *MPEP*, § 2164.07. When the enablement question rests on whether the disclosure is sufficient to satisfy the how-to-use requirement of the first paragraph of 35 U.S.C § 112, the PTO must have adequate support for its challenge to the credibility of applicant's statements as to utility; only then does the burden shift to applicant to provide rebuttal evidence. *In re Bundy*, 642 F.2d 430, 433, 209 U.S.P.Q.48, 51 (CCPA 1981); See also *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995).

The Examiner has not met his initial burden. Applicants have demonstrated that Val^{8}-GLP-1, which is representative of a class of DPP IV protected analogs, can be administered by pulmonary means as evidenced in the examples. (For example see p. 33 of Applicants' specification) The Examiner's evidence or reasoning that Applicants' have failed to comply with the enablement provision of § 112 is a naked assertion that GLP-1 peptides in serum are only fragments of inactive peptides when

administered to the lung, thus, rendering the peptide not "useful." The Deacon et al. reference (*Diabetologia* 41, 271,1998), cited by the Examiner, fails to provide any evidence to cause one of skill in the art to question Applicants' asserted enablement of GLP-1 peptide when administered by pulmonary means. The focus of the Deacon et al. reference is to examine whether modifications of the N-terminus of GLP-1 would confer resistance to degradation by dipeptidyl peptidase IV (DPP IV). The assay employed by Deacon et al. was used to show that N-terminus modifications actually resulted in less degradation of the peptide as compared to a non-modified N-terminus. DPP IV resistant analogs have higher percentage of intact peptide *in vivo*, longer half-life *in vivo*, and are biologically active. Applicants recognized the benefit of a DPP IV resistant analog and so stated in their application, "administration of GLP-1 analogs and derivatives that are protected from the activity of DPP IV is preferred, and the administration of Gly^{8}-GLP-1(7-36)NH_2, Val^{8}-GLP-1(7-37)OH, alpha-methyl-Ala^{8}-GLP-1(7-36)NH_2, and Gly^{8}-Gln^{21}-GLP-1(7-37)OH, or pharmaceutically-acceptable salts thereof, is more preferred." (See p. 9, line 25 to p. 10, line 2). The Examiner has not met his burden of providing sufficient reasons for doubting Applicants' assertions that Val^{8}-GLP-1 or other DPP IV protected GLP-1 analogs can be effectively administered by pulmonary means.

REJECTION UNDER 35 U.S.C. § 112 SECOND PARAGRAPH

The Examiner rejected Claims 19, 23, 33, and 44-69 under 35 U.S.C. §112 second paragraph for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 19, 23, and 33 were rejected for reciting the term "effective dose," rendering the claims indefinite "as to the objective(s) of efficacy." Applicants respectfully submit that this rejection is inappropriate and request reconsideration and withdrawal of the rejection. The Applicants define effective dose in the specification. "GLP-1 related compounds described above are administered by inhalation in a dose effective manner to introduce circulating therapeutic levels which results in reducing abnormally high blood glucose levels." (See p. 12 line 30 to p.13 line 15). Further, the MPEP addresses this issue and states that the phrase "effective amount" is definite when read in light of the supporting disclosure. (MPEP § 2173.05(c)). Based on Applicants' specification, the ordinary skilled person would understand that effective dose means to administer enough Val^{8}-GLP-1 or other DPP IV protected GLP-1 analogs by inhalation such that Val^{8}-GLP-1 or other DPP IV protected GLP-1 analogs will be absorbed into the circulation and have the effect of lowering blood glucose.

Claim 19 was rejected as indefinite as to "the process step(s) intended." As previously mentioned Applicants state that "GLP-1 related compounds described above are administered by inhalation in a dose effective manner to introduce circulating therapeutic levels which results in reducing abnormally high blood glucose levels." (See p. 12 line 30 to p.13 line 15). Thus, the ordinary skilled person would understand that the process encompasses administering enough Val^{8}-GLP-1 or other DPP IV protected GLP-1 analogs by inhalation such that Val^{8}-GLP-1 or other DPP IV protected GLP-1 analogs will be absorbed into the circulation and have the effect of lowering blood glucose.

Claim 51, which recites the term "MMAD" was rejected as indefinite for not being defined. The specification defines

"MMAD" as mass median aerodynamic diameter (See p. 14 line 7). Claims that provide a MMAD limitation have been amended such that the definition now appears in the claims, thus, rendering the rejection moot.

Claim 51, which recites "less than about 10 microns" was rejected as indefinite as to which term dominates, the "about", or the "less than"? Applicants offer that since 1996 more than 12,000 U.S. patents have issued with "less than about" language in the claim, and more than 15,000 U.S. patents have issued with "at least about" language in the claim. Further the MPEP addresses this issue and suggests that these types of phrases are definite when read in light of the supporting disclosure. (MPEP § 2173.05(b)(A)).

Claims 55, 58, and 64 which recite the phrase "capable of depositing" were rejected as indefinite as to whether the deposition takes place or not. Applicants have amended the claims by replacing "capable of depositing" with "deposited," thus, rendering the rejection moot.

Claims 61-63 and 66-69 which recite "an actuation . . . administers" were rejected as indefinite as to "how many different actuations are there". Applicants have amended the claims by removing the word "an," thus, rendering the rejection moot.

REJECTION UNDER 35 U.S.C. § 103

The Examiner rejected Claims 19, 23, 33, and 44-69 under 35 U.S.C. §103 as being unpatentable over Drucker (USP 5846937) in view of Galloway (USP 5705483); or Smith (USP 5908830) in view of Galloway; or Knudsen (WO 98/20895) in view of Galloway; or Gelfand (EP 0619322) in view of Galloway; or Kirk (WO 93/18785) in view of Galloway. The Examiner states that the Drucker, Smith, Knudsen, or Gelfand reference teach administration of GLP peptides by pulmonary means and the Kirk

reference teaches nasal administration of GLP peptides, while Galloway teaches that Val^{8}-GLP-1 resists the proteolytic action of DPP-IV. The Examiner concludes that it would have been obvious to one of ordinary skill to administer Val^{8}-GLP-1 to a patient by pulmonary means. Applicants request reconsideration and withdrawal of the rejection.

The United States Supreme Court stated that to make out a case of obviousness, one must: "(1) determine the scope and content of the prior art; (2) ascertain the differences between the prior art and the claims in issue; (3) determine the level of skill in the pertinent art; and (4) evaluate any evidence of secondary considerations." *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). In addition, to support a *prima facie* case of obviousness over a combination of prior art references, the Examiner must establish that the prior art contains a suggestion or motivation to combine the prior art references in such a way as to achieve the claimed invention. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). The Federal Circuit has also in several cases stated that hindsight is not a justifiable basis on which to find an invention obvious. *See In re Dembiczak*, 175 F.3d 994 (Fed. Cir. 1999).

> Measuring a claimed invention against the standard established by section 103 requires the oft-difficult but critical step of casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field.

Id. at 999. Thus, to avoid a hindsight analysis wherein the inventor's teachings are used against him, "there must be a rigorous application of the requirement for showing the teaching or motivation to combine the prior art references." *Id.* The Examiner's case must also include a finding that one of ordinary skill in the art at the time the invention was

made would have reasonably expected the claimed invention to work. *See In re O' Farrell*, 853 F.2d 894 (Fed. Cir. 1988). Further, it is inconsistent for the examiner to argue that the references render the invention obvious and at the same time express doubt at the Applicants' ability to show the usefulness of the claimed invention. *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986).

In this case, none of the cited references explicitly or implicitly teach, suggest, or motivate a skilled person to combine the references and arrive at the invention without using Applicants' specification. The Drucker reference actually provides examples of intracerebroventricular (ICV) injections to demonstrate the claimed method of sedating a mammalian subject. (See examples 2 and 4). The Smith reference relates generally to a combination therapy that does not even need a GLP-1 peptide to be included in the claimed composition. (See col 19, lines 50-55). Thus, Smith does not teach pulmonary delivery of any specific compound. The Knudsen reference lists routes of administration including subcutaneous injections, intramuscular injections, intraperitoneal injections, intravenous injections, infusion pumps, nasal spray, "pulmonal" spray, transdermal, buccal, rectal, and vaginal, while the Gelfand reference lists routes of administration including subcutaneous injections, intramuscular injections, infusion pumps, nasal inhalation, oral inhalation, transdermal, and gastrointestinal. Such laundry lists would not lead those skilled in the art to believe that any or all of these routes of administration suggest or motivate administering Val^{8}-GLP-1 or other DPP IV protected GLP-1 analogs by pulmonary means. Finally, the Kirk reference relates to administration of a GLP-1 peptide and a phospholipid by an intranasal route. Intranasal delivery is not pulmonary delivery.

In addition, the second prong of the United States Supreme Court's test for obviousness requires the Examiner to look at the differences between the scope and content of the prior at and the claims in issue. *Graham*, 383 U.S. at 17. The Examiner has failed to apply the second prong of the test. Not only do the cited references fail to provide any teaching, suggestion or motivation to those skilled in the art to administer Val^{8}-GLP-1 or other DPP IV protected GLP-1 analogs by pulmonary means, they further fail to provide particle sizes, formulations, how to inhale, the type of device, where the particles are deposited, the amount deposited, the doses, or the diseases treated. Nowhere in the cited references are these additional limitations mentioned. Therefore, the scope and content of the cited references fail at suggesting or motivating those skilled in the art to arrive at Applicants' claimed invention.

Furthermore, the cited references (Drucker, Smith, Knudsen, Gelfand, or Kirk) either by themselves or with the Galloway reference do not establish a reasonable likelihood that any GLP-1 peptide could be expected to be administered by pulmonary means. In rejecting Applicants' invention for lack of enablement, the Examiner expressed doubt as to whether intact and active GLP-1 peptides appear in the serum. Thus, the Examiner admits that the cited references do not provide a reasonable expectation of success. In fact the cited references do not even focus on or contain any experimental details regarding administration of *any GLP-1* by pulmonary means, but rather merely contain a generic boilerplate type statement regarding various routes of administration. However, Applicants have shown that GLP-1 peptides can be administered by pulmonary means and absorbed into the blood. Efficient pulmonary delivery is dependent on the ability to deliver the peptide to the deep lung alveolar epithelium. Peptide particles that lodge in the upper airway epithelium

are not absorbed to a significant extent because the overlying mucus functions to trap and clear debris by mucociliary transport up the airway. This mechanism is also a major contributor to low bioavailability. Thus, there is no reasonable expectation that GLP-1 peptides would pass into the blood when administered by pulmonary means. Applicants' data demonstrate that the Val^{8}-GLP-1 deposited lung dose had 40% bioavailability relative to subcutaneous injection. (See p. 30 of the specification). Thus a case of obviousness cannot be supported. The references cited by the Examiner do not explicitly or implicitly teach, suggest, or motive the present invention with any expectation of success.

SUMMARY AND CONCLUSION

In conclusion, in view of the remarks provided herein above, it is respectfully submitted that the Examiner has not met his burden to establish that Applicants' have not enabled one skilled in the art to make and/or use the invention. The Examiner's assertion that there is no evidence that the peptide is 'useful' is not supported by any evidence or reasoning as required by the Federal Circuit. The claims are definite and particularly point out and distinctly claim the subject matter being sought. Further, the Examiner has also failed to establish a *prima facie* case of obviousness. Without using Applicant's specification, there is no teaching, suggestion, or motivation that a GLP-1 peptide can be successfully administered by pulmonary means. Even the Examiner questioned the expectation of success in his

enablement rejection. Reconsideration and withdrawal of the rejections are therefore requested.

Respectfully submitted,

Gregory A. Cox
Agent for Applicants
Registration No. 47,504
Phone: 317-277-2620

Eli Lilly and Company
Patent Division/GAC
Lilly Corporate Center
Indianapolis, Indiana 46285

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